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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/103,745	06/24/1998	SUDHIR AGRAWAL	IDRA-740US1	3401

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KEOWN & ZUCCHERO, LLP
500 WEST CUMMINGS PARK
SUITE 1200
WOBURN, MA 01801

EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/103,745	AGRAWAL, SUDHIR	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date. _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/4/2009 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 3/4/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 9/4/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Also acknowledged are Applicant's amendments to the claims, filed 3/4/2009. With entry of the amendment, claims 16-19 are pending and examined herein.

Claim interpretation

The specification teaches at page 8 that for purposes of the invention the term "phosphorothioate oligonucleotide" means an oligonucleotide containing at least one phosphorothioate internucleoside linkage, and that "a CpG dinucleoside is "modified" if it is altered from the unmodified CpG dinucleoside such that it confers upon the oligonucleotide a reduced ability to cause splenomegaly and platelet depletion."

The specification teaches at page 11 that "A 2'-0-substituted CpG is a CpG dinucleoside in which the 2' position of the pentose moiety is substituted," and that "[m]ost preferably, the 2'-0-Substituted CpG is a 2'-0-methyl cytosine containing CpG, or a 2'-0-methyl guanosine containing CpG or both."

Accordingly, the instant claims embrace oligos having one or more phosphorothioate linkages and one or more CpG dinucleotides in which either the C or G or both in each of said dinucleotides is 2'-O substituted.

Oligonucleotides having these structural features are considered to have all properties inherent to such oligonucleotides, including those recited in the claims, as a chemical and its physical/biochemical properties are inseparable. An oligonucleotide having each of the structural characteristics recited in the claims would necessarily also have the physical and chemical properties inherent to such compounds, including those recited in the claims. Burden is shifted to applicant to show otherwise. MPEP 2112.

Thus, for purposes of the prior art rejections below, functional limitations such as "reduced side effects" and "fewer side effects" are considered to represent nothing more than the inherent intrinsic properties of modified CpG-containing phosphorothioate oligonucleotides. While the prior art may not have recognized this property at the time, it is not necessary under 35 USC 102 or 103 that all properties inherent to a prior art compound be disclosed along with compound, so long as the compound and a method for making said compound was disclosed.

As explained below, modified CpG-containing phosphorothioate antisense oligonucleotides, wherein all CpG dinucleotides present in the oligo were modified, and methods for using said oligonucleotides in mammals were known in the prior art.

The claims require no minimum level of gene expression inhibition. Thus, the limitation "for which inhibition of expression is desired" in claim 16 embraces any level of inhibition. Claims 17-19 require no inhibitory activity.

The limitations "reduced side effects" and "fewer side effects" do not require the complete absence of side effects. Any reduction, even a fraction of 1%, relative to the unmodified oligonucleotide is within the scope of the claim.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 16-19 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,476,000.

U.S. Patent No. 6,476,000 claims a method for reducing the immunostimulatory effect of a CpG-containing oligonucleotide, the method comprising introducing a 2'-substituted

nucleoside into the oligonucleotide at a position adjacent to, and on the 5' side of the CpG dinucleoside, wherein at least one nucleoside is a deoxyribonucleoside, and the oligonucleotide is not complementary to the gag or rev gene of human immunodeficiency type 1, wherein only one 2' substituted nucleoside is introduced into the oligonucleotide for each CpG dinucleotide present in the oligonucleotide, thereby producing an oligonucleotide having a reduced immunostimulatory effect relative to a CpG-containing oligonucleotide that does not comprise a 2'-substituted nucleoside at a position adjacent to, and on the 5' side of the CpG dinucleoside. With regard to the claimed subject matter, the specification states the term "2" substituted" means substitution of the 2' position of the pentose moiety with a halogen (preferably Cl, Br, or F), or an —O-lower alkyl group containing 1-6 saturated or unsaturated carbon atoms. The instant claims embrace at least one species of these 2'-substituted oligonucleotides as defined by the conflicting claims. Implicit to the claimed method of the conflicting patent is the administration of the modified oligonucleotides to a subject or organism having an immune system which might otherwise adversely react to the unmodified oligonucleotide.

Therefore, one of ordinary skill in the art would conclude that the invention defined in the claims at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting patent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawasaki et al. (1993) *J. Med. Chem.* 36:831–841 in view of:

1. Agrawal et al. (WO 94/01550); and
2. Shillitoe et al. (1994) *Cancer Gene Therapy* 1:193–204.

Kawasaki et al. disclosed a 15-nucleotide, human papilloma virus genome-specific, CpG-containing antisense oligonucleotide, comprising a phosphorothioate backbone in which each CpG is 2'-O-methyl modified (see oligo #12 in Table 1, page 833). Compositions thereof are also disclosed and tested (see pages 833–840).

Kawasaki et al. did not teach steps for administering Oligo #12 of Table 1 to a mammal.

However, Kawasaki et al. explicitly recognized the antisense, RNase H activity of each of the chimeric oligos disclosed therein, including the 2'-O-methyl modified, papilloma virus-specific oligo 12 set forth in Table 1, and, on the basis of their studies, suggest applying the oligos against biological targets (page 837, right column).

Agrawal et al. set forth methods and materials for making and using self-stabilized, phosphorothiote antisense oligonucleotides against virtually any known viral or cellular gene, and specifically taught and suggested methods for administering such oligos to animals and humans for therapeutic purposes to treat a diseased human or animal in which the disease results from infection with the virus or pathogenic organism. The method comprises administering self-stabilized oligonucleotides according to the invention in a pharmaceutically acceptable carrier to the diseased human or animal (page 18 and claims 18-20).

Shillitoe et al. teach that papilloma viruses are etiological agents of cancer, and are often present in many cervical and oral cancers.

It would therefore have been prima facie obvious to one of skill in the art at the time of invention to make and administer any of the Kawasaki et al. antisense oligonucleotides, including olig #12, according to the methods taught by Agrawal et al. to treat cervical or oral cancer caused by human papilloma virus by specifically inhibiting the expression and function of the papilloma viral genome in the manner shown by Kawasaki et al.

One would have been well motivated and have had a reasonable expectation of success given that Kawasaki et al. taught that the oligos disclosed therein possess antisense activity against human papilloma virus, given that Agrawal et al. taught that chemically modified, self-stabilized antisense oligos are more resistant to nuclease degradation and more potent than conventional single-stranded antisense oligonucleotides, that such oligos are effective for treating viral infections, and that such oligos may be administered to humans for the treatment of viral infections, and given that Shillitoe et al. taught that papilloma viruses may be the underlying cause of some forms of human cancer.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

***

Claims 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monia et al. (US Patent 5,563,255).

Monia et al. disclosed several different 2'-O-methyl modified CpG-containing phosphorothioate antisense oligonucleotide, 20-nucleotides in length, complementary to the human c-raf gene for inhibition of said gene in cells in vitro and in vivo, wherein all CpG dinucleotides present in the oligonucleotides are 2'-O-methyl modified (see, for example, ISIS 6712, 6720, 6717, 6729, and 9271 in Tables 2-5, cols. 10-15; and disclosure cols. 1-20). Several are recommended for inhibiting the expression of c-raf mRNA (see cols 11-13). Several were said to inhibit c-raf expression by at least 70% when tested (col. 11).

Monia et al. contemplate but do no specifically exemplify the use of the cited oligonucleotides in a mammal or individual with a disease.

However, Monia et al. taught the use of said chimeric anti-c-Raf antisense oligonucleotides for research and therapeutic purposes in cells in vitro and in vivo to inhibit the expression of c-raf in cells and thereby inhibit cell proliferation in culture and in mammals (cols. 1-20). Monia et al. taught the association between c-raf expression and cancer, or abnormal cell proliferation (cols. 1-5). Monia et al. taught that oligonucleotides of their invention may be used to inhibit gene expression in cells in culture and in animals, as is common in research and development work investigating oncogenes (see examples in cells and nude mice at columns 15-

20). Monia et al further taught the c-raf antisense oligonucleotides may be used as therapeutics and formulated for oral, intravenous, subcutaneous, or intraperitoneal administration (col. 8 and see examples at cols. 15-20). Monia et al. showed that ISIS oligonucleotides 5132, a PS antisense lacking 2'-O-methyl modifications but otherwise identical to the chimeric oligos cited in the 35 USC 102 rejection above, may be administered by intraperitoneal injection to nude mice having T24 human bladder and human breast carcinoma tumor xenografts (cols. 17 and 18). The oligo was said to inhibit tumor growth in said mice models (cols. 13 and 14).

Accordingly, it would have been prima facie obvious to one of skill at the time of invention to make and use any of the Monia et al. 2'-O-methyl modified phosphorothioate anti-raf antisense oligonucleotides in animals and individuals for research and therapeutic purposes to inhibit tumor cell growth and investigate c-raf expression as it relates to tumor cell growth in vivo. As each of the olignucleotides were clearly shown to be effective for inhibiting c-raf expression in tumor cells in culture, and in view of the exemplary embodiment of ISIS 5132, representative of the SEQ ID NO:8 and modified variants thereof, demonstrating its use in vivo, one of skill would have reasonably predicted that each of ISIS oligos 6720, 6717, and 6729, for example (discussed at cols. 11 and 12), could be used in the same manner to produce similar if not superior results in a nude mouse or individual comprising said tumor cells.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Response to Arguments

Applicant traverses the instant rejections together on the following grounds: 1) the references do no teach modifying all CpG dinucleotides present in an oligonucleotide, and 2) the references do not teach or recognize that modifying all CpG dinucleotides in an oligonucleotide would reduce side effects of CpG-containing oligonucleotides. Applicant asserts the use of inherency in the rejection of a claimed process under 35 USC 103 is proper only if the inherency of such a feature would have been known or obvious at the time the invention was made.

Applicant's arguments have been fully considered but are not persuasive.

The Examiner notes that inherency is a question of fact (MPEP 2112). Inherency is relevant to both anticipation and obviousness. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

In the instant case, it is undisputed that the prior art—Kawasaki et al. and Monia et al.—disclosed antisense phosphorothioate oligonucleotides in which each of the CpG dinucleotides present are 2'-O-methyl modified in the manner required by the claims. Thus, the oligonucleotides in the prior art are structurally indistinguishable from those recited in the instant claims. Therefore, these oligonucleotides necessarily have all properties inherent to such compounds, as a compound and its properties are inseparable. As the prior art expressly recommends using these compounds to inhibit gene expression and treat disease associated with said gene in animals and subjects, including each step of the instant claims, one of skill practicing the methods of using said oligonucleotides in the manner recommended by the prior

art would necessarily obtain all effects inherent to such methods, including those recited in the instant claims (reduced side effects of splenomegaly and depletion of platelets).

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

A practitioner seeking to make and use any of the oligonucleotides disclosed in Kawasaki or Monia for the purposes recommended therein (research or treatment of disease), or by other references, would obtain all the effects and advantages of such oligonucleotides, whether recognized or not. Because the suggestion to make and use the oligonucleotides in the manner suggested by prior art does not rely on a recognition of those properties specifically recited in the claims (reduced side effects) as the motivating factor, it is not necessary for the prior art to have specifically recognized those properties, as argued by applicant. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)

Prior art made of record but not currently relied on

Monia et al. (1993) *J. Biol. Chem.* 268:14514-14522 disclosed the benefits of using chimeric phosphorothioate 2'-O-methyl subsitituted oligonucleotides that contain between 5 and 9 centered 2'-deoxy residues flanked by 4 to 6 2'-O-methyl substituted nucleotides on the 5' and

3' ends, or wings (pp. 14516-14522; Fig. 1 and 4). Such compounds are said combine the favorable aspects of PS-oligonucleotides (RNase H activation) and 2'-O-methylribonucleotides (nuclease and duplex stability), resulting in increased potency (page 14514-5 and 14520-2).

In one exemplary embodiment (Fig. 1, Fig. 3, and Fig. 4), Monia et al. disclosed a phosphorothioate CpG-containing oligonucleotide complementary to a human Ha-ras gene, having a 3-nucleotide deoxy gap in which each CpG dinucleotide comprises at least one 2'-O-methyl modified C or G or both (see the oligo fourth from the top in Fig. 1).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Primary Examiner, Art Unit 1635
April 24, 2009